REMARKS

Restriction Requirement

The Examiner has maintained the Restriction Requirement. Non-elected Claims 28-47 have been cancelled without prejudice to or disclaimer of the subject matter therein. Applicants expressly reserve the right to pursue the subject matter of the non-elected claims in divisional applications without the need to file a terminal disclaimer. Claims directed to non-elected species are still pending in anticipation of allowance of a generic claim. Applicants again assert that the invention is not limited to the elected species.

Objection to the Specification:

The Examiner has objected to the "Brief Description of the Drawings", contending that the specification refers to Fig. 2A-2E and Fig. 3A-3F, while only Figs. 2 and 3 have been submitted. Applicants have amended the specification to more correctly reference the drawings.

Rejection of Claims 1-7, 16 and 24 Under 35 U.S.C. § 112, Second Paragraph:

The Examiner has rejected Claims 1-7, 16 and 24 under 35 U.S.C. § 112, second paragraph, contending that these claims are indefinite due to the use of the phrase "potentially binds to". To expedite prosecution, Applicants have amended Claim 1 to remove the term "potentially" found objectionable by the Examiner.

In view of the foregoing amendments, the Examiner is respectfully requested to withdraw the rejection of Claims 1-7, 16 and 24 under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 1-7 and 24 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1-7 and 24 under 35 U.S.C. § 103, contending that these claims are unpatentable over Mond et al. in view of Prodinger et al. and further in view of Hampton Research. Specifically, the Examiner contends that Mond et al. disclose vaccine adjuvants that bind to the CR2 complex containing EBV gp350/220. The Examiner contends that Mond et al. disclose a method for identifying Gp350/220 analogs that may bind to CR2 and inhibit its binding to CR2 natural ligands, including determining the portion of the three-dimensional structure of CR2 that

binds to gp350 220. The Examiner acknowledges that Mond et al. do not teach the three-dimensional structure of CR2 SCR1-2, but submits that Prodinger et al. characterize a monoclonal antibody that binds to CR2 and allegedly identifies the importance of the SCR1-2 region in ligand binding. Therefore, the Examiner contends that it would have been obvious to crystallize the SCR 1-2 region in light of Mond et al. to identify compounds that inhibit binding of CR2 to its ligands. Additionally, the Examiner asserts that one would have a reasonable expectation of success because protein crystallization would have become routine in the field, citing a crystal screening kit marketed by Hampton Research.

Applicants traverse the rejection of Claims 1-7 and 24 under 35 U.S.C. § 103. It is well established that for a rejection under § 103 to be proper, all the claim limitations must be **taught or suggested** by the prior art. *In re Royka*, 180 USPQ 580 (CCPA, 1970). Applicants submit that the claimed invention requires the ability to provide and use the three-dimensional structure of the SCR1-SCR2 region of CR2 in order to perform the method steps. The determination by the present inventors of the three dimensional structure of the SCR1-SCR2 region of CR2 enables one of skill in the art to the practice the present invention and represents a novel and non-obvious discovery, as discussed below. Applicants submit that the combination of references cited by the Examiner not only fails to teach or suggest the elements of the present invention, the combination further fails to provide the requisite expectation of success to make and use the invention as claimed.

More specifically, the Examiner asserts that the combination of Mond et al. and Prodinger et al. are sufficient to teach the crystallization of the short consensus repeats (SCR) 1 and 2 of CR2 and methods of identifying compounds that inhibit the binding of CR2 to its ligands, the expectation of success being provided by the Hampton Research catalog and its Crystal Screen® kit. Applicants submit that not only does the combination of Mond et al. and Prodinger et al. not teach or suggest the claimed three-dimensional structure of the SCR1-SCR2 region of CR2 (and therefore also cannot teach or suggest a method of using such a structure), the combination of references, with or without the Hampton Research catalog, absolutely fails to provide a reasonable expectation of success of arriving at the claimed invention.

Initially, Applicants note that a method to crystallize CR2 is not presently being claimed. Rather, what is claimed is a method of identification of compounds using the three dimensional

structure of CR2 as provided by the present invention. The combination of Mond et al. and Prodinger et al., alone or in combination with the Hampton Research catalog, fail to teach or suggest the three dimensional structure of CR2 as claimed. The Examiner acknowledges that Mond et al. do not teach or suggest the three-dimensional structure of CR2 SCR1-2. Applicants further submit that not only is Mond et al. lacking in this particular teaching, Mond et al. provide absolutely no teaching or suggestion of *how* one can produce or determine the three-dimensional structure of CR2, *what* portions of CR2 should be crystallized for this determination, or *how* one could analyze what portions of CR2 bind to Gp350/220. Indeed, Mond et al. clearly do not know where Gp350/220 binds to CR2 (see column 7, lines 20-28), and even suggest that Gp350/220 and C3d may bind to two different regions on CR2 (see column 3, lines 18-20), which is known by the present invention to be incorrect. Mond et al. is directed to EBV Gp350/220 and variants thereof for providing vaccine adjuvants, and provides no teaching regarding CR2 other than that EBV binds to CR2. Therefore, Mond et al. provide no guidance for actually attempting to produce a three dimensional structure of CR2 and at best, the reference represents a simple invitation to further experimentation.

The Examiner's combination must therefore rely on Prodinger et al. to provide all of the information necessary to arrive at the three dimensional structure of CR2. However, Applicants submit that Prodinger et al. also do not teach or suggest the correct three dimensional structure of CR2 and thus, even when combined with Mond et al., can not teach or suggest the present invention. A teaching of "the importance of the [SCR1-SCR2] region in ligand binding" as cited by the Examiner is not a teaching or suggestion of the three dimensional structure of CR2 according to the present invention, nor a teaching or suggestion of how to determine this structure. Applicants acknowledge that it has been proposed in the art for years that the binding site between CR2 and C3d lies within the SCR1-SCR2 region of CR2. However, this information simply does not teach or suggest the three dimensional structure of CR2, or what portions of the SCR1-SCR2 region of CR2 actually bind or interact with C3d.

Prodinger et al. attempt to map the C3d binding site in the SCR1-SCR2 region of CR2 using a peptide array, but fail to teach or suggest the actual three dimensional structure of CR2, and in fact teach a model that can now be shown to be incorrect by the present invention. This provides a *teaching away* from the present invention and a demonstration that the determination of the three

dimensional structure of CR2 is not a simple or obvious discovery. More specifically, Prodinger et al. propose a model of SCR1-SCR2 wherein the CR2 ligand (e.g., C3d) binds to a recess formed between SCR1 and SCR2 (see the abstract, Fig. 5 and the Discussion). As can clearly be seen from the disclosure in the present invention, this model and the proposed binding sites (see Prodinger et al. abstract) are not correct. Referring to Figs. 1A and 1B of the present invention, the ligand binding site for CR2 is not in the recess between SCR1 and SCR2 at all, but rather is found primarily between other sites on SCR2 and the ligand. Therefore, the incorrect model of Prodinger et al. is not useful in methods for identifying or designing regulatory compounds, and it is clear that the combination of Mond et al. and Prodinger et al. do not teach or suggest each and every element of the claimed invention.

It appears that in the present case the only suggestion for the Examiner's combination of the teachings improperly stems from the Applicants' own disclosure and not from the cited references themselves. To draw on hindsight knowledge of the invention, when the prior art does not contain or suggest that knowledge, is to use the invention as a template for its own reconstruction -- an illogical and inappropriate process by which to determine patentability. W.L. Gore & Assoc. v. Garlock, Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983). The invention must be viewed not after the blueprint has been drawn by the inventor, but as it would have been perceived in the state of the art that existed at the time the invention was made. Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985). The Examiner has provided no basis in the art for the knowledge of the three dimensional structure of a CR2 protein. To merely cite a reference that states the desirability of having the three dimensional structure is not sufficient evidence that one of ordinary skill in the art would have found the present method obvious.

With regard to the introduction of the Hampton Research catalog by the Examiner as alleged evidence of a reasonable expectation of success at arriving at the claimed invention, Applicants again submit that a method to crystallize CR2 is not being claimed. Rather, what is claimed is a method of identification of compounds using the three dimensional structure of CR2 as provided by the present invention. In any event, the suggestion that the Hampton Research catalog makes it routine in the art to crystallize any protein is completely unfounded. The Crystal Screen® kit produced by Hampton Research is merely a kit that supplies a variety of premade buffers, precipitants and

additives for rapidly screening for conditions under which it is *possible* that a given protein will crystallize. The kit is only a first step reagent, because once a set of possible conditions is identified, the investigator must then experiment on his/her own within a more narrow range of conditions to actually crystallize the protein. Therefore, the kit is helpful only as a first guidance tool toward defining some crystallization conditions with which to experiment, but does not actually allow an investigator to simply mix a protein with a reagent and suddenly crystallize a protein. The Examiner seems to imply that crystallization of a protein and the subsequent determination of the three dimensional structure is routine, but this is completely unsupported by the state of the art at the time of the invention.

At best, the Examiner's comments regarding obviousness appear to amount to an assertion that one of ordinary skill in the relevant art would have been able to arrive at Applicants' invention because they would have had the necessary skills to carry out the requisite process steps. This is an inappropriate standard for obviousness. "A statement that modifications of the prior art to meet the claim limitations would have been 'well within the ordinary skill of the art at the time the invention was made', because the cited references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993)." MPEP 2143.01. In this case, the Examiner has not even provided evidence that all aspects of the claimed invention were individually known in the art.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-7 and 24 under 35 U.S.C. § 103.

Rejection of Claims 1-7, 16 and 24 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1-7, 16 and 24 under 35 U.S.C. § 103, contending that these claims are unpatentable over Mohammadi et al. Specifically, the Examiner contends that Mohammadi et al. discloses the crystal structure of a protein tyrosine kinase and shows a method of performing a computer analysis to identify an agent that binds to and modulates the protein tyrosine kinase. The Examiner contends that the process of Mohammadi et al. differs from the instant invention only in the content of the crystal coordinates. The crystal coordinates are alleged to be

non-functional descriptive material and therefore, the Examiner asserts that the structural coordinates are not given any patentable weight over Mohammadi et al.

Applicants traverse the Examiner's rejection of Claims 1-7, 16 and 24 under 35 U.S.C. § 103. Since the Examiner clearly acknowledges that Mohammadi et al. do not teach or suggest the crystal coordinates of CR2, this rejection relies solely on the Examiner's apparent position that the claimed process differs from the prior art only with respect to non-functional descriptive material that can not alter how the process steps are to be performed to achieve the utility of the invention (emphasis added). Applicants submit that this is clearly not a fair or accurate reading of the presently claimed invention. The claims recite a method for the identification of compounds that bind to complement receptor type 2 (CR2) proteins or to a complex of CR2 and its ligand. The method steps require the provision of the three dimensional structure of the CR2 short consensus repeat (SCR) 1-2 region and the use of the three dimensional structure to identify a candidate compound for binding to the CR2 SCR 1-2 region.

Applicants are not claiming a method to store atomic coordinates on a computer or a computer that contains the atomic coordinates. A method to store atomic coordinates on a computer might be analogous to the example of storing a song on a disk (provided by the MPEP), but the claimed method has completely different process steps that lead to the utility of the invention. Applicants are claiming a method of structure-based identification of compounds which requires the use of a specific structure to achieve the utility of the invention. Without intending to discuss whether or not atomic coordinates are non-functional descriptive material, even assuming, *arguendo*, that atomic coordinates for a given protein are non-functional descriptive material, the claimed method does not differ from Mohammadi et al. solely with respect to this material. One simply can not perform the steps of the claimed method using the atomic coordinates of Mohammadi et al. and *achieve the utility of the invention*, demonstrating that the method requires more than the atomic coordinates themselves. Indeed, the provision of the three dimensional structure of CR2 SCR1-2 region completely alters how the remaining process steps are performed (i.e., the identification of candidate compounds for binding to CR2).

More specifically, the claimed method requires the provision of the three dimensional structure of the CR2 SCR 1-2 region, followed by the use of the structure to identify compounds.

In order to provide the three dimensional structure, one must perform some active step of causing the provision, supply, display, or retrieval of *the three dimensional structure* of the CR2 SCR 1-2 region, such as by using a software program to manipulate the atomic coordinates and produce a model of the structure. Then, one must perform an additional step of using this structure (e.g., the model) to actively identify and/or design candidate compounds for binding to the CR2 SCR 1-2 region. If one used the atomic coordinates of Mohammadi et al. and then proceeded to attempt to provide a three dimensional structure of CR2 SCR1-2 region, one would obviously fail completely. Moreover, one certainly would not be able to achieve the utility of identifying compounds that bind to the CR2 region using a three dimensional structure for a *protein tyrosine kinase*.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-7, 16 and 24 under 35 U.S.C. § 103.

Applicants have attempted to address the Examiner's concerns as set forth in the December 18 Office Action. The Examiner is encouraged to contact the below-named agent with any questions or concerns regarding Applicants' position.

Respectfully submitted,

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Date: March 17, 2003